We Claim:

1. A method for inhibiting bone metastases and metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

2. The method of Claim 1 wherein the bone metastases are osteoblastic.

3. The method of Claim 2 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

4. The method of Claim 3 wherein the primary cancer is prostate cancer and the patient is male.

5. The method of Claim 1 which additionally comprises co-administeration of an anticancer drug.

6. The method of Claim 5 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

7. The method of Claim 1 which additionally comprises the administeration of radiation therapy.

8. The method of Claim 1 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

9. The method of Claim 8 wherein the therapeutic agent is a bisphosphonate.

10. The method of Claim 1 wherein the endothelin antagonist is an $ET_A$-selective endothelin antagonist.

11. A method for the inhibition of bone loss in a

patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

12. The method of Claim 11 wherein the patient has cancer.

13. The method of Claim 11 wherein the cancer is prostate cancer and the patient is male.

14. The method of Claim 11 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

15. The method of Claim 14 wherein the therapeutic agent is a bisphosphonate.

16. A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

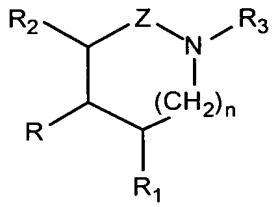
17. The method of Claim 16 wherein the cancer is prostate cancer and the patient is male.

18. The method of Claim 16 which additionally comprises the administeration of an anticancer drug.

19. The method of Claim 18 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

20. The method of Claim 17 which additionally comprises the administeration of radiation therapy.

21. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

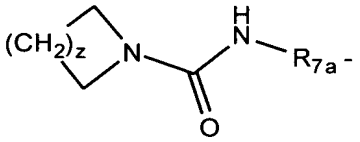
Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

$R_1$ and $R_2$ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of $R_1$ and $R_2$ is other than hydrogen;

$R_3$ is selected from $R_4$-C(O)-$R_5$-, $R_4$-$R_{5a}$-, $R_4$-C(O)-$R_5$-N($R_6$)-, $R_6$-S(O)$_2$-$R_7$- $R_{26}$-S(O)-$R_{27}$-, $R_{22}$-O-C(O)-$R_{23}$-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and $R_{13}$-C(O)-CH($R_{14}$)-;

$R_4$ and $R_6$ are independently selected from ($R_{11}$)($R_{12}$)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



$R_5$ is selected from a covalent bond, alkylene, alkenylene, -N($R_{20}$)-$R_8$-, -$R_{8a}$-N($R_{20}$)-$R_8$-, -O-$R_9$-, and -$R_{9a}$-O-$R_9$-;

$R_6$ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

$R_7$ is a covalent bond, alkylene, alkenylene -N($R_{21}$)-

$R_{10}$-, and -$R_{10a}$-N($R_{21}$)-$R_{10}$-;

$R_8$ is selected from alkylene and alkenylene;

$R_9$ is alkylene;

$R_{10}$ is selected from alkylene and alkenylene;

$R_{11}$ and $R_{12}$ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

$R_{13}$ is selected from amino, alkylamino and dialkylamino;

$R_{14}$ is selected from aryl and $R_{15}$-C(O)-;

$R_{15}$ is selected from amino, alkylamino and dialkylamino;

$R_{16}$ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

$R_{17}$ is loweralkyl;

$R_{18}$ and $R_{19}$ are independently selected from hydrogen and loweralkyl;

$R_{20}$ is selected from hydrogen, loweralkyl, alkenyl,

haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

$R_{21}$ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

$R_{22}$ is selected from a carboxy protecting group and heterocyclic;

$R_{23}$ is selected from covalent bond, alkylene, alkenylene and $-N(R_{24})-R_{25}-$;

$R_{24}$ is selected from hydrogen and loweralkyl;

$R_{25}$ is alkylene;

$R_{26}$ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

$R_{27}$ is selected from alkylene and alkenylene;

$R_{5a}$ is selected from alkylene and alkenylene;

$R_{7a}$ is alkylene;

$R_{8a}$ is selected from alkylene and alkenylene;

$R_{9a}$ is alkylene;

$R_{10a}$ is selected from alkylene and alkenylene;

$R_{aa}$ is selected from aryl and arylalkyl;

$R_{bb}$ is selected from hydrogen and alkanoyl;

$R_{cc}$ is alkylene;

m is 0-6;

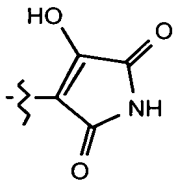
n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$, -CN, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,



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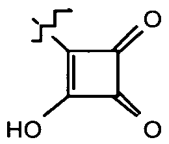

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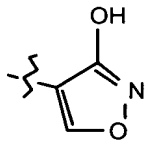

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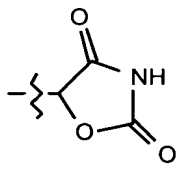

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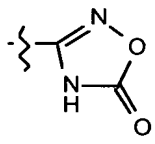

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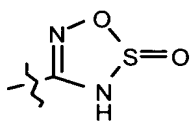

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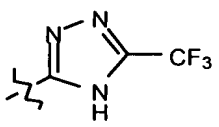

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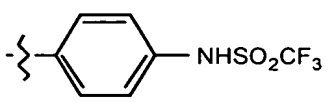


,

or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21 wherein the bone metastases are osteoblastic.

23. The method of Claim 22 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

24. The method of Claim 23 wherein the primary cancer is prostate cancer and the patient is male.

25. The method of Claim 21 which additionally comprises the administeration of an anticancer drug.

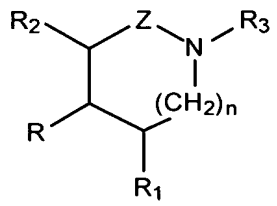
26. The method of Claim 25 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

27. The method of Claim 21 which additionally comprises the administeration of radiation therapy.

28. The method of Claim 21 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

29. The method of Claim 28 wherein the therapeutic agent is a bisphosphonate.

30. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:




I

wherein

R is $-(CH_2)_m-W$;

Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

$R_1$ and $R_2$ are independently selected from hydrogen,

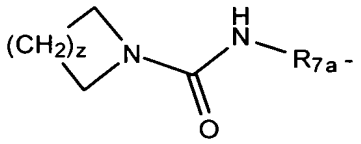
loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of $R_1$ and $R_2$ is other than hydrogen;

$R_3$ is selected from $R_4-C(O)-R_5-$, $R_4-R_{5a}-$, $R_4-C(O)-R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$ $R_{26}-S(O)-R_{27}-$, $R_{22}-O-C(O)-R_{23}-$, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and $R_{13}-C(O)-CH(R_{14})-$;

$R_4$ and $R_6$ are independently selected from $(R_{11})(R_{12})N-$, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic,

(heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



$R_5$ is selected from a covalent bond, alkylene, alkenylene, $-N(R_{20})-R_8-$, $-R_{8a}-N(R_{20})-R_8-$, $-O-R_9-$, and $-R_{9a}-O-R_9-$;

$R_6$ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

$R_7$ is a covalent bond, alkylene, alkenylene $-N(R_{21})-R_{10}-$, and $-R_{10a}-N(R_{21})-R_{10}-$;

$R_8$ is selected from alkylene and alkenylene;

$R_9$ is alkylene;

$R_{10}$ is selected from alkylene and alkenylene;

$R_{11}$ and $R_{12}$ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy,

aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

$R_{13}$ is selected from amino, alkylamino and dialkylamino;

$R_{14}$ is selected from aryl and $R_{15}$-C(O)-;

$R_{15}$ is selected from amino, alkylamino and dialkylamino;

$R_{16}$ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

$R_{17}$ is loweralkyl;

$R_{18}$ and $R_{19}$ are independently selected from hydrogen and loweralkyl;

$R_{20}$ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

$R_{21}$ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

$R_{22}$ is selected from a carboxy protecting group and heterocyclic;

$R_{23}$ is selected from covalent bond, alkylene, alkenylene and -N($R_{24}$)-$R_{25}$-;

$R_{24}$ is selected from hydrogen and loweralkyl;

$R_{25}$ is alkylene;

$R_{26}$ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

$R_{27}$ is selected from alkylene and alkenylene;

$R_{5a}$ is selected from alkylene and alkenylene;

$R_{7a}$ is alkylene;

$R_{8a}$ is selected from alkylene and alkenylene;

$R_{9a}$ is alkylene;

$R_{10a}$ is selected from alkylene and alkenylene;

$R_{aa}$ is selected from aryl and arylalkyl;

$R_{bb}$ is selected from hydrogen and alkanoyl;

$R_{cc}$ is alkylene;

m is 0-6;

n is 0 or 1;

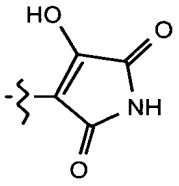
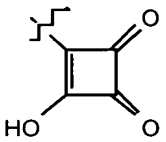
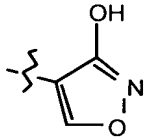
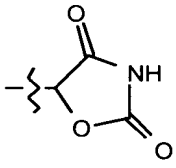
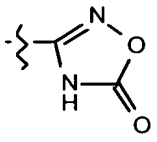
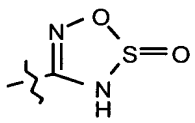
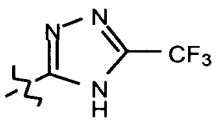
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting

group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$, -CN, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,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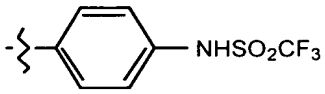


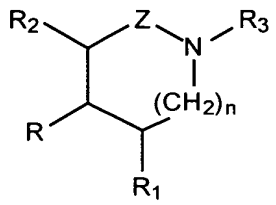
or a pharmaceutically acceptable salt thereof.

31. The method of Claim 30 wherein the cancer is prostate cancer and the patient is male.

32. The method of Claim 30 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

33. The method of Claim 32 wherein the therapeutic agent is a bisphosphonate.

34. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

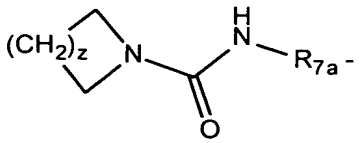
$R_1$ and $R_2$ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl,

alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of $R_1$ and $R_2$ is other than hydrogen;

$R_3$ is selected from $R_4-C(O)-R_5-$, $R_4-R_{5a}-$, $R_4-C(O)-R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$ $R_{26}-S(O)-R_{27}-$, $R_{22}-O-C(O)-R_{23}-$, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and $R_{13}-C(O)-CH(R_{14})-$;

$R_4$ and $R_6$ are independently selected from $(R_{11})(R_{12})N-$, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



$R_5$ is selected from a covalent bond, alkylene, alkenylene, $-N(R_{20})-R_8-$, $-R_{8a}-N(R_{20})-R_8-$, $-O-R_9-$, and

$-R_{9a}-O-R_9-$;

$R_6$ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

$R_7$ is a covalent bond, alkylene, alkenylene $-N(R_{21})-R_{10}-$, and $-R_{10a}-N(R_{21})-R_{10}-$;

$R_8$ is selected from alkylene and alkenylene;

$R_9$ is alkylene;

$R_{10}$ is selected from alkylene and alkenylene;

$R_{11}$ and $R_{12}$ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl,trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

$R_{13}$ is selected from amino, alkylamino and dialkylamino;

$R_{14}$ is selected from aryl and $R_{15}-C(O)-$;

$R_{15}$ is selected from amino, alkylamino and dialkylamino;

$R_{16}$ is selected from loweralkyl, haloalkyl, aryl and

dialkylamino;

$R_{17}$ is loweralkyl;

$R_{18}$ and $R_{19}$ are independently selected from hydrogen and loweralkyl;

$R_{20}$ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

$R_{21}$ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

$R_{22}$ is selected from a carboxy protecting group and heterocyclic;

$R_{23}$ is selected from covalent bond, alkylene, alkenylene and $-N(R_{24})-R_{25}-$;

$R_{24}$ is selected from hydrogen and loweralkyl;

$R_{25}$ is alkylene;

$R_{26}$ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

$R_{27}$ is selected from alkylene and alkenylene;

$R_{5a}$ is selected from alkylene and alkenylene;

$R_{7a}$ is alkylene;

$R_{8a}$ is selected from alkylene and alkenylene;

$R_{9a}$ is alkylene;

$R_{10a}$ is selected from alkylene and alkenylene;

$R_{aa}$ is selected from aryl and arylalkyl;

$R_{bb}$ is selected from hydrogen and alkanoyl;

$R_{cc}$ is alkylene;

m is 0-6;

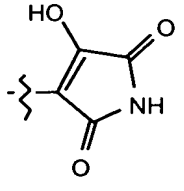
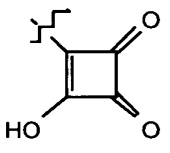
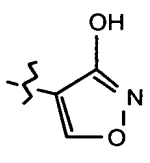
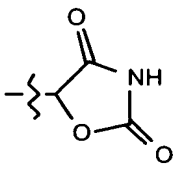
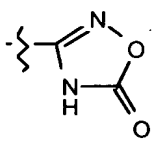
n is 0 or 1;

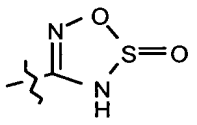
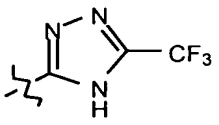
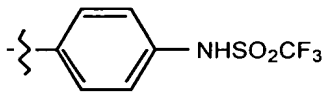
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$, $-CN$, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,

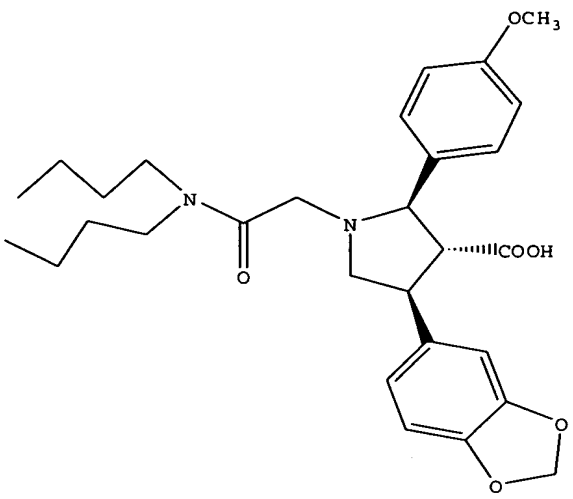
or a pharmaceutically acceptable salt thereof.

35. The method of Claim 34 wherein the cancer is prostate cancer and the patient is male.

36. The method of Claim 34 which additionally comprises the administration of an anticancer drug.

37. The method of Claim 36 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

38. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III




III.

39. The method of Claim 38 wherein the bone metastases are osteoblastic.

40. The method of Claim 39 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

41. The method of Claim 40 wherein the primary cancer is prostate cancer and the patient is male.

42. The method of Claim 40 which additionally comprises the administeration of an anticancer drug.

43. The method of Claim 42 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

44. The method of Claim 40 which additionally comprises the administeration of radiation therapy.

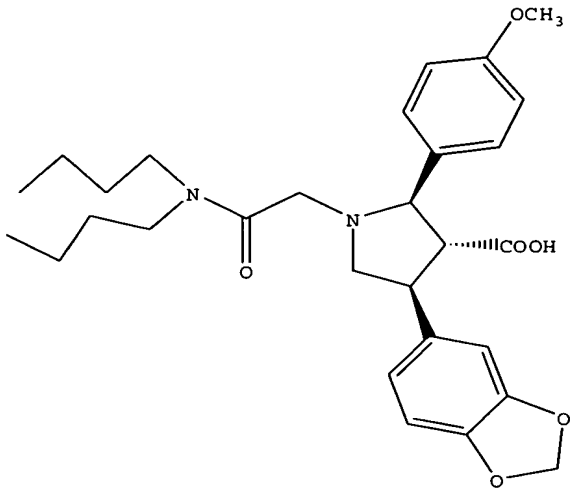
45. The method of Claim 40 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

46. The method of Claim 45 wherein the agent is a bisphosphonate.

47. The method of Claim 40 wherein the endothelin antagonist is an $ET_A$-selective endothelin antagonist.

48. A method for the inhibition of bone loss in

cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III



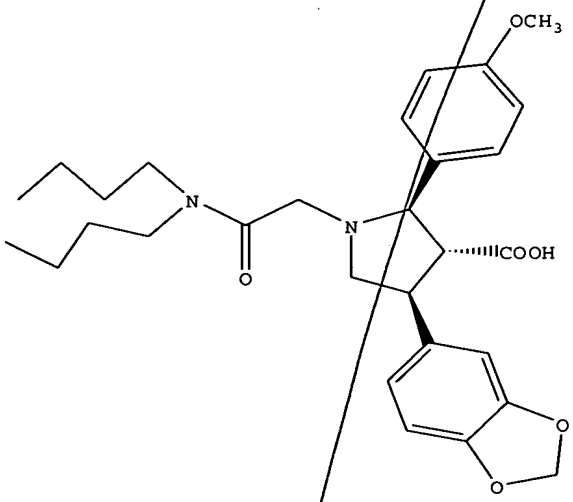

III.

49. The method of Claim 48 wherein the cancer is prostate cancer and the patient is male.

50. The method of Claim 48 which additionally comprises the administeration of at least one therapeutic agent which impedes net bone loss.

51. The method of Claim 50 wherein therapeutic agent is a bisphosphonate.

52. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula III




III.

53. The method of Claim 52 wherein the cancer is prostate cancer and the patient is male.

54. The method of Claim 52 which additionally comprises the administeration of an anticancer drug.

55. The method of Claim 54 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D

analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

56. A method for preventing new bone metastases in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

57. A method for inhibiting metastatic growth in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

58. A method for inhibiting bone turnover in a patient which comprises administring to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.